Remarks/Arguments:

This is a reply to the office action of March 7.

The claims have been amended above to properly state the Markush groupings. The limitations of claim 24 have been added to claim 21. Minor editorial changes have also been made.

The non-elected claims (32 - 40) have been canceled without prejudice to the filing of a divisional application thereon. Claims 41 and 42 are new, and are directed to the elected species of keratolytic agent.

The present invention relates to a formulation comprising a keratolytic agent, particularly trichloroacetic acid, and dimethyl isosorbide as a penetration enhancer. The composition is used for attaining an efficacious chemical peeling.

Peeling, particularly chemical peeling, stimulates cellular turnover by removing dead cells from the corneous layer, by eliminating damaged and degenerated epidermal cells and by inducing an inflammatory reaction with activation of the mediators of the inflammation, which, in turn, activates the production of new collagen fibers and glycosaminoglycans, thus revitalizing the dermis.

Chemical peeling carries a risk of complications and undesired outcomes, so it is important to carry out treatments and therapies which achieve excellent results with the least possible risk. Such excellent results, accompanied by low or even no risks at all, are surprisingly and unexpectedly achieved by the composition of the present invention, as defined in the claims above.

Claims 21 - 28 stand rejected as obvious over U.S. Patent 5166176 ('176) and 5824326 ('326) in combination.

The '176 patent relates to a composition comprising trichloroacetic acid, a surfactant and a humectant-emollient possessing peeling activity. Tricholoroacetic acid provides the keratolytic activity, and the two other components are added to prevent the uneven peeling obtained if trichloroacetic acid alone is used. In particular, said surfactant is a saponin. Saponin is added because it has a cell growth stimulatory activity and since it causes the acidic component to be evenly and thoroughly distributed across the treated area of the skin. This reference does not teach the use of a penetration enhancer compound to improve the activity of the keratolytic agent as claimed in the present application.

Patent '326 concerns a cosmetic composition in which the known penetration enhancer dimethyl isosorbide has been introduced to enhance the skin activities of ferulic acid and its esters. The patent describes in particular anti-tanning performance of such a composition. Patent '326 does not refer to chemical peeling compositions. Dimethyl isosorbide is introduced given the known difficulty of delivering ferulic acid and its derivatives into the skin (see column 1, line 28-30). The composition described in '326 does not provide any peeling activity, such effect or purpose not being mentioned.

The present invention enhances, by means of dimethyl isosorbide, the penetration of the keratolytic agent to prevent skin damage. The skilled person would not consider using a penetration enhancer in combination with a keratolytic agent, in particular trichloroacetic acid, due to the well known aggressive nature of such treatments and the need to repair the damages caused by the strong effect of this acid compound.
In fact, Patent '176 combines trichloroacetic acid with saponin that have a cell growth stimulatory activity, with the clear aim of protecting and repairing the treated skin. However, the addition of a cell growth stimulatory agent with pharmacological

activity may lead to unwanted side effects. In particular, an increase of cell growth may cause mutagenic effects or undesired overproliferation.

The present invention provides a method wherein the undesired damages of the skin by using a keratolytic agent are avoided, without resorting to a supplementary pharmaceutical treatment.

This is not suggested or taught by the cited prior art. Thus, the use of dimethyl isosorbide, which is well documented by experimental data in the description of the present application, is a non-obvious selection from a very broad group of agents that potentially can cause damage to the skin by acting as penetration enhancer.

We therefore submit that claim 21 recites a peeling composition which is new and non-obvious from the prior art.

Claim 21 describes the use of a keratolytic agent together with a penetration enhancer in a rate comprised between 1:4 and 4:1. Dimethyl isosorbide is contained as a penetration enhancer in the composition disclosed in patent '326 from 0.1 to 20% by weight, which is below the percentage claimed by the present application. The prior art does not disclose or suggest using a penetration enhancer in such high percentage in a cosmetic composition, or in a peeling composition. Thus claim 21 is deemed patentable over the prior art.

Dependent claims 22 - 28 are deemed patentable for the features they inherit from claim 21, in combination with the additional features recited in those dependent claims.

Claims 29 - 31 were rejected as obvious of the '176 and '326 patents, further in view of WO 94/05301, which discloses compositions comprising dimethyl sulfone, which

we agree is also called methyl sulfonyl methane or MSM. The reference indicates that the MSM intensifies the therapeutic effect of a combination of salicylic acid and sulphur, when used as a treatment for "housewife dermatitis". There is no indication that MSM alone would have therapeutic benefit, or that it would intensify the effect of combinations of other chemicals selected for their skin peeling qualities. It therefore is submitted that WO 94/05301 would not have led one of ordinary skill in the art to add dimethyl sulfone to the peeling composition of the present invention.

New claims 41 - 42 are limited to the elected species of keratolytic agent (trichloro-acetic acid), and are deemed patentable for reasons presented above with respect to claims 21 and 29 - 31.

We believe the claims now presented are patentable over the prior art of record, and that this application is now in condition for allowance.

Respectfully submitted,

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